REMARKS/ARGUMENTS

Support for Amendments

Support for each amendment is provided throughout the original application, including the specification and drawings, as originally filed. Exemplary passages are provided in support of each amendment.

Claim 1 is amended to recite:

each electrode array comprises at least two electrode structures, and further wherein each the electrode structure comprises at least two electrode elements and the electrode element width is between 1.5 and 15 times the width of the electrode gap;

a plurality of connection pads located on said substrate, wherein each connection pad is in electrical communication with at least one of said electrode structures; and

wherein said device has a surface suitable for cell attachment or growth and said cell attachment or growth on said device results in a detectable change in impedance between or among said electrode structures.

Support may be found in paragraph [0036], which reads, in part,

> Figure **1A** is a schematic representation of a device 100 with two electrode structures of same or similar areas deposited on a substrate. First electrode structure has electrode elements 110a, 110b, 110c and second electrode structure has electrode elements 120a, 120b, 120c and 120d.

Additional support may be found in paragraph [00175], which reads, in part,

> "In the present application, it is preferred that the electrode gap between electrode elements should be designed with respect to the electrode width. While other ratios of the electrode element width to gap may be utilized, preferably, the ratio of electrode element width to gap width is between about 1:3 and 20:1. Preferably, the electrode element width is between 1.5 and 15 times the gap width.

Additional support may be found in paragraph [00239], which reads, in part, "In yet another aspect... at least two connection pads on said substrate, wherein said at least two electrodes are connected respectively to said at least two connection pads... solution."

Additional support may be found in paragraph [00153], which reads, in part, "Preferably, cell attachment or growth on the surface of any of the electrodes or electrode structures in the above devices results in detectable change in impedance between or among said electrodes or electrode structures."

Claim 7 is amended to recite, *the electrode elements of each electrode structure are of equal widths.*

Support may be found in paragraph [0029], which reads, in part, "The electrodes of each electrode array may be of equal widths."

Claim 8 is amended to recite,

The device according to Claim 1 for detecting cells on an electrode surface through measurement of impedance changes resulting from attachment of said cells to said electrode surface, wherein electrode elements' widths are between about 0.5 times and about 10 times the size of cells used.

Support may be found in paragraph [00174], which reads, in part,

> "Preferably, an electrode element's width is between about 0.5 times and about 10 times the size (e.g., the width of an average cell when it spreads and attaches to the substrate) of cells used in an assay that uses the device."

Claim 9 is amended to recite, *electrode elements' widths are in the range between 20 micron and 500 micron.*

Support may be found in paragraph [00175], which reads, in part, "More preferably, the electrode width is in the range between 20 micron and 500 micron."

Claims 11 and 12 were amended to correct dependency.

Claim 13 is amended to recite, *wherein at least one bus is associated with up to half of the plurality of electrode elements in the at least two electrode structures of each electrode array.*

Support may be found in paragraph [0030], which reads, in part, "In one embodiment, at least one bus encircles up to half of the plurality of interdigitated electrodes in each electrode array." Further support may be found in paragraph [0031], which reads, in part, "In one embodiment, at least one bus encircles up to half of the plurality of concentrically organized electrodes in each electrode array."

Claims 19 and 21 were amended to correct dependency.

Claim 22 is amended to recite, *The device according to Claim 21 for detecting cells on an electrode surface through measurement of impedance changes resulting from attachment of said cells to said electrode surface, wherein electrode elements' widths are between about 0.5 times and about 10 times the size of cells used.*

Support may be found in paragraph [00174], which reads, in part,

> "Preferably, an electrode element's width is between about 0.5 times and about 10 times the size (e.g., the width of an average cell when it spreads and attaches to the substrate) of cells used in an assay that uses the device."

Claim 23 is amended to recite, *The device according to Claim 21 for detecting cells on an electrode surface through measurement of impedance changes resulting from attachment of said cells to said electrode surface, wherein electrode elements' widths are in the range between 20 micron and 500 micron.*

Support may be found in paragraph [00175], which reads, in part, "More preferably, the electrode width is in the range between 20 micron and 500 micron."

Claim 24 is amended to recite,

The device according to Claim 21 for detecting cells on an electrode surface through measurement of impedance changes resulting from attachment of said cells to said electrode surface, wherein the gap between electrode elements of the electrode structures ranges from 0.2 time and 3 times the width of an averaged cell used.

Support may be found in paragraph [00173], which reads, in part,

> "While other gap dimensions may be used, preferably, the gap between electrode elements of the electrode structures ranges from about 0.2 times and 3 times the width of an average cell used in an assay using the device."

Claim 25 is amended to recite, *an impedance analyzer electrically connected to all or a plurality of the electrical connection pads.*

Support may be found in paragraph [00185], which reads, in part, "The present apparatuses can further comprise one or more impedance analyzer connected to one or more connection pads."

Claims 31 and 32 are amended to recite, *wherein less than all of the containers are associated with at least one of said plurality of electrode arrays.*

Support may be found in paragraph [0047], which reads, in part,

> "Figure **12(A)** shows a device having 15x electrode-structure units were arranged in a 2-row by 8-column configuration on a substarte. .... One of the wells is a "null" well; that is, there is no active sensor associated with that well. The null well is utilized as a control well...."

Support may further be found in paragraph [0186], which reads, in part,

> "In other embodiments, not all the wells have electrode structures for impedance-based monitoring of molecular reactions. Thjis is particularly useful when the electrodes are made of optically non-transparnet materials. ...... Similarly, with the plate in **Figure 16(B),** the 92 wells permit the impedance-based monitoring of the cells whilst the four corner wells are electrode-structure free so that the cells grown or cultured in these wells can serve as controls, and can be monitored using inverted, optical microscope."

Claim 36 is amended to recite, *wherein the electrode arrays are individually addressed.*

Support may be found in paragraph [00190], which reads, in part,

> "In still another embodiment, at least one pair of the electrodes or one pair of electrode arrays of the present apparatuses is individually addressed in terms of connecting to an impedance analyzer or an impedance measurement circuit."

Claim 40 is amended to recite, *an impedance analyzer and connection means for establishing electrical communication between the connection pads and the impedance analyzer.*

Support may be found in paragraph [00185], which reads in part,

> "The present apparatuses can further comprise one or more impedance analyzer connected to one or more connection pads. Electrode can directly or indirectly connect to a connection pad, where they connect to a line from a signal source."

Claim 48 is amended to correct dependency.

Claim 72 is amended to recite,

electrode elements and gaps between said electrode elements are arranged so that there is a more than 50% probability for cells to contact an electrode element when said cells are introduced onto said device.

Support may be found in paragraph [00128], which reads, in part,

> "As used herein, a "high probability of contacting an electrode element" means that, if a cell is randomly positioned within the sensor area of a device or apparatus of the present invention, the probability of a cell (or particle) contacting on an electrode element, calculated from the average diameter of a cell used on or in a device or apparatus of the present invention, the sizes of the electrode elements, and the size of the gaps between electrode elements, is greater than about 50%, more preferably greater than about 60%, yet more preferably greater than about 70%, and even more preferably greater than about 80%, greater than about 90%, or greater than about 95%

Claim 287 is newly added and recites,

The device according to Claim 1 for detecting cells on an electrode surface through measurement of impedance changes resulting from attachment of said cells to said electrode surface, wherein the gap between electrode elements of electrode structures ranges from 0.2 time and 3 times the width of an averaged cell used.

Support may be found in paragraph [00173], which reads, in part,

> "While other gap dimensions may be used, preferably, the gap between electrode elements of the electrode structures ranges from about 0.2 times and 3 times the width of an average cell used in an assay using the device."

Claim 288 is newly added and recites,

The device according to Claim 1 for detecting cells on an electrode surface through measurement of impedance changes resulting from attachment of said cells to

said electrode surface, wherein the gap between electrode elements of the electrode structures is between about 3 microns and 80 microns.

Support may be found in paragraph [00173], which recites, in part,

> "Preferably, the width of a gap between electrodes or electrode elements of a device of the present invention used for monitoring eukaryotic cells, such as mammalian cells, such as cancer cells, endothelial or epithelial cells, is between about 3 microns and 80 microns. . . microns."

Claim 289 is newly added and provides,

The device according to Claim 21 for detecting cells on an electrode surface through measurement of impedance changes resulting from attachment of said cells to said electrode surface, wherein the gap between electrode elements of the electrode structures is between about 3 microns and 80 microns.

Support may be found in paragraph [00173], which reads, in part,

> "Preferably, the width of a gap between electrodes or electrode elements of a device of the present invention used for monitoring eukaryotic cells, such as mammalian cells, such as cancer cells, endothelial or epithelial cells, is between about 3 microns and 80 microns... microns."

<u>Response to Rejections / Objections</u>

I. Response to Rejections/Objections under 35 U.S.C. §112

A. The Examiner rejected claims 48-50 and 72 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter in which Applicant regards as the invention.

More specifically the Examiner notes that claims 48-50 depend from canceled claim 53. Applicants have amended claims 48-50 to depend from pending claim 47. Thus Applicants respectfully request this rejection be withdrawn.

The Examiner alleges the term "high" in claim 72 is a relative term which renders that claim indefinite. Although the specification as originally filed provides a description of the term "high" that would render the claim definite, Applicants have substituted the term "high probability" to "more than 50%" to expedite allowance. Thus Applicants respectfully request the rejection be withdrawn.

II. Response to Rejections / Objections under 35 U.S.C. §103

A. The Examiner has rejected claims 1-4, 6-10, 25-28, 33, 36, 38-40, 43-46 and 72 under 35 U.S.C. §103(a) as being unpatentable over Kovacs (US 6,051,422) in view of Facer (US 2003/0072549).

With respect to claims 1, 8, 9, 36, 43 and 72 the Examiner alleges the following. Kovacs discloses a microelectronic cell sensor array comprising a non-conductive substrate (FIG 6:69) and at least one electrode array (FIG 6:68) positioned on the substrate. FIGS 3 and 4 disclose embodiments in which a plurality of electrode arrays (34) are provided for cell detection. FIGS 7-9 indicate that each electrode array includes a plurality of individual electrodes that are separated from each other by an area of non-conductive material. A reference electrode (FIG 3:31) is in communication with the electrode arrays to assist in measuring cell impedance. See col. 3, ln. 43 to col. 5, ln. 19, col. 7, lns. 17-23, col. 8, lns. 31-34, col. 9, lns. 24-38 and col. 12, lns. 36-62. Additionally Kovacs teaches that the electrically conductive traces extend from bond pads at the opposing ends of the substrate, and are in communication with the electrode arrays. This is described in col. 4. lns. 60-66 and illustrated in FIGS 7-9. Kovacs, however does not expressly state that the electrodes in each array have a width of more than 1.5 to 10 times the width of the non-conductive area between the electrodes.

The Examiner adds that Facer discloses a device for detecting cells that comprises a non-conductive substrate (FIG 1:12) and a plurality of conductive elements (FIGS 14, 16) positioned on the substrate. Paragraph [0012] states that a gap (FIG 1:20) is made in the inner conductor through which biological solutions are allowed to pass. Changes in impedance across the gap are then detected using the conductive elements. Paragraphs [0027]-[0033] give exemplary ranges of sizes and widths for the conductive elements and the gap. Facer suggest that the conductive elements have a width of approximately 40 microns, and that the gap constituting the area between the conductive elements is characterized by a width of 1 to 10 microns.

Thus the Examiner argues that at the time of the invention, it would have been obvious to one of ordinary skill in the art to alter Kovac's device to ensure that the electrode widths were more than 1.5 and less than 10 times the non conductive material width if it was determined through trial and error that this configuration produced the best results. The limitation is considered to be a result effective variable that is optimized through routine experimentation. The position is supported by Facer, who indicates in paragraph [0033] that electrode width and gap sizes all depend on several considerations that involve engineering tradeoffs. Facer implies that it is known in the art to consider a variety of width sizes in order to produce the best configuration for the current experiment.

Applicants' Response

Claims 1, 8, 9, 36, 43 and 72 are not obvious over Kovacs (US 6,051,422) in view of Facer (US 2003/0072549) prior to amendment; however, to expedite allowance of the present application Applicants have amended claim 1, from which claim 8, 9, 36, 43 and 72 depend, to recite, "*each electrode structure comprises at least two electrode elements and the electrode element width is between 1.5 – 15 times the width of the electrode gap* " and to recite, "*wherein the device has a surface suitable for cell attachment or growth and the cell attachment or growth results in a detectable change in impedance between or among the electrode structures*."

Although Applicants acknowledge the technologies disclosed in Kovacs (US 6,051,422) and Facer (US 2003/0072549) both involve microelectronics, each technology

operates using substantially different principles than that of the present invention and from one another and therefore operate in substantially different ways. Thus a combination of Kovacs and Facer does not yield the technical features found in Applicants' invention nor would one skilled in the present art contemplate the combination of the Kovacs and Facer technologies to produce a technology as disclosed in the present invention. Moreover, optimization of the Kovacs' technology would not result in Applicants' invention because of the substantial differences in approaches between the technologies.

For the convenience of the Examiner, Applicants provide the following general discussion of the Kovacs, Facer and Applicants' technologies to assist in the clarification of substantial differences in the approaches used in the microelectronic monitoring of cells.

First, referring to FIG. 1 of US 6,051,422, the Kovacs technology includes a reference electrode (31) and an array of microelectrodes (34), which are also referred to in the specification as measuring electrodes. Importantly Kovacs states,

> "[T]he relative size of the reference electrode is large in comparison to the measuring electrodes so that the measured impedance across each electrode and the reference electrode is dominated by the interface between the microelectrode and the cell and the cell membrane impedance." Col. 7, ln. 58-63.

In Kovacs, an electrical signal is applied selectively between each of the microelectrodes and the reference electrode. Col. 7, ln 20-24. The signals are detected at the reference electrode. Col. 7, ln 25. Therefore in essence, Kovacs provides a device that includes an array of microelectrodes that are *singly and selectively activated in combination with a central large reference electrode.* The fluctuations in impedance are due to interactions with the single, selected microelectrode because of the large relative size difference between large reference electrode and the particular activated microelectrode.

In contrast the present invention does *not* incorporate *a reference electrode that is large in comparison* to microelectrodes. Unlike Kovacs, the present invention utilizes a

plurality of electrode arrays, each having a plurality of electrode structures, which further include at least two electrode elements. Moreover, unlike Kovacs, the present invention does not require the *selective application* of an electrical signal between a microelectrode and *a large reference electrode.*

Next, referring to FIG. 1 of (US 2003/0072549), the Facer technology utilizes a technology referred to in the industry as Co-Planar Waveguide (CPW). More specifically the Facer technology incorporates *one inner conductor flanked by two outer conductors.* Para [0011].

In contrast, the present invention does not utilize CPW. The present invention utilizes a plurality of electrode arrays, each having a plurality of electrode structures, which further include at least two electrode elements. Thus, unlike Facer, the present invention does *not* require on *inner conductor flanked by two outer conductors.*

Now referring more specifically to claim 1 of the present invention, Applicants' invention includes *a plurality of electrode arrays, each including at least two electrode structures, further wherein each electrode structure comprises at least two electrode elements. The electrode element width is between 1.5 to 15 times the width of the electrode gap.* Neither Kovacs nor Facer alone or in combination discloses this technology.

Applicants' incorporate herein Applicants' description of Kovacs and Facer in support of Applicants' position that neither Kovacs nor Facer alone or in combination provide *a plurality of electrode arrays, each including at least two electrode structures, further wherein each electrode structure comprises at least two electrode elements.*

In addition, neither Kovacs nor Facer alone or in combination disclose *the electrode element width is between 1.5 to 15 times the width of the electrode gap,* as provided in Applicants' Clam 1. In Kovacs, there are arguably two types of gaps: 1) those between the microelectrodes themselves; and 2) those between the microelectrodes and the large reference electrode. The microelectrode to microelectrode gap ratio is of little consequence because the electrical signal is *selectively applied between a single microelectrode and a large reference electrode.* (*See* FIG. 3 and col. 10, ln 9-12 and claim 1). Again, Kovacs does not stimulate the entire array of microelectrodes but instead only one of a plurality of microelectrodes is stimulated in combination with the

large reference electrode. Thus, the only gap arguably of any importance would have to be the spacing between the microelectrode and the large reference electrode.

When evaluating a width to gap ratio incorporating a microelectrode to large reference electrode gap as provided in Kovacs, it would first have to be determined whether the electrode width is: 1) the large reference electrode width; or 2) the microelectrode width because there is no discussion of such a width to gap ratio in Kovacs. As referred to above,

> "*[T]he relative size of the reference electrode is large in comparison to the measuring electrodes so that the measured impedance across each electrode and the reference electrode is dominated by the interface between the microelectrode and the cell and the cell membrane impedance.*" Col. 7, ln. 58-63.

Since the reference electrode is sufficiently large such that the microelectrode interface "dominates", only a change in width of the microelectrode will be addressed.

Before addressing any variations in microelectrode width, it should be noted that with reference to the FIGS in Kovacs, the gap between each microelectrode and the large reference electrode is much larger than the width of the particular microelectrode whereas in the present invention, the gap between electrode elements is smaller than the width of the electrode element.

However, even if the Kovacs' microelectrode width was varied in relation to the gap between the microelectrode and large reference electrode, it would take unreasonable experimentation to pursue such as course. As can be seen in FIG. 1 and as stated throughout the specification, there are multiple microelectrodes *selectively activated* for measurement with the large reference electrode. Thus, *the microelectrode to large reference electrode gap varies significantly depending on which microelectrode is activated.* Thus each gap and microelectrode width would have to be considered for the entire array. Yet there is no guidance or suggestions as to varying the sizing of *each and every* microelectrode across the entire array to accommodate the variety of possible gaps. From the FIGS, it appears that all Kovacs' electrodes are of the same size and do not vary, which would contradict varying the width of a microelectrode with respect to its varying position in relation to the large reference electrode.

The disclosure regarding the gap appears limited to an example where a 100 micron pitch was disclosed for a 6x6 array of 10 micron diameter microelectrodes. However Kovacs did not address the sizing of the microelectrode widths in relation to their varying position with relation to the large reference electrode. It is disclosed that the impedance electrodes are designed specially for monitoring individual cells (col. 3, ln. 42-col 4,ln 60) and thus there is a special requirement that the *diameter of the cell is larger than the diameter of the microelectrode* (col. 5, ln.4-6) so that each microelectrode is sufficiently small to monitor an individual cell and its cellular membrane (col. 7, ln. 55-58). Therefore it is apparent that a cell is larger than the microelectrode.

Again, based on the geometries shown in the FIGS, the gap between the microelectrode and the reference electrode is *larger* than the microelectrode width, which contradicts the current position of the Examiner. Thus, in summary Kovacs the sizing of the microelectrode width is dependent on: 1) being much smaller than the large reference electrode; 2) being smaller than the diameter of a cell; and 3) being smaller than the microelectrode to large reference electrode gap. Therefore it would not be obvious to adapt Kovacs, alone or in combination, to Applicants' invention, even absent Kovacs' requirement of a large reference electrode.

Now referring to Facer, the Facer technology incorporates CPW and utilizes *one inner conductor flanked by two outer conductors*. Para [0011]. The Examiner refers to Para [0012], which states that a gap (FIG 1:20) is made in an inner conductor through which biological solutions are allowed to pass. However, the gap in Facer is different than the gap in Applicants' invention. In Facer, the gap is a passageway that exists between two inner conductor segments, which are electrically connected on *one* measurement line on the impedance analyzer (the external conductor being the other measurement line). Therefore applying the Facer gap to Kovacs, it appears Kovacs would require yet another gap that acts as a passageway through a single microelectrode.

In contrast, the gap disclosed in the present invention is not a passageway between two inner conductor segments, which are electrically connected on *one* measurement line on the impedance analyzer, but instead spacing between electrode elements. For example, in paragraph [0172], the gap is described as

> "the gap that extends in the plane of the substrate (in the direction normal to the major axis of the gap) from where it borders one electrode element to where it borders the other electrode element on its opposite side."

As a brief review, Applicants' invention includes electrode structures having at least two electrode elements. The electrode element width is between 1.5 and 15 times the width of the electrode gap. In Applicants' invention, the gap is positioned between electrode elements that connect to different measurement lines on the impedance analyzer. Thus, the discussion of the gap in Facer does not apply to the gap included in the present invention.

The Examiner argues that Facer, in paragraph [0033], discloses electrode width and gap sizes all depend on several considerations that involve engineering tradeoffs. Indeed, engineering tradeoffs are common in many technologies. However, engineering tradeoffs referred to in Facer would provide engineering tradeoffs of the Facer gap, which significantly differs from the gap in Applicants' invention (see discussions above). However even if the Kovacs' microelectrode width was varied in comparison to Kovacs' gap (the gap between each microelectrode and large reference electrode) the present invention would still not be obvious. Although there may be engineering tradeoffs, the requirements of Kovac's system include a *large reference electrode* and microelectrodes that are *singly* and *individually* activated. Moreover there is no suggestion that varying the Kovacs' gap would yield any beneficial results since the technological approach emphasizes the size differences between the large reference electrode and microelectrode.

In view of the arguments setforth above, it should be apparent a combination of Kovacs in view of Facer would <u>not</u> render *the electrode element width is between 1.5 and 15 times the width of the electrode gap* obvious.

Applicants cancel claim 6, 27, 28 and 33 to economize on USPTO fees.

With respect to claims 2-4, 7-10, 25, 26, 36, 38-40, and 43-46, Applicants incorporate herein Applicants' arguments previously setforth above in claim 1, from which claims 2-4, 7-10, 25, 26, 36, 38-40 and 43-46 depend.

For the reasons setforth above, claims 1-4, 6-10, 25-28, 33, 36, 38-40, 43-46 and 72 are not obvious over Kovacs (US 6,051,422) in view of Facer (US 2003/0072549) prior to or after amendment and Applicants' respectfully request the rejections be withdrawn.

B. The Examiner has rejected claims 1-3, 8-10, 36, 40-43 and 72 under 35 U.S.C. §103(a) as allegedly being upatentable over Sugihara (US 6,132,683) in view of Facer (US 2003/0072549).

The Examiner provides the following arguments in support of the 35 U.S.C. §103(a) rejection. With respect to claims 1, 8, 9, 36, 43 and 72, Sugahara (US 6,132,683) discloses a microelectronic cell sensor array comprising a substrate (FIG. 2:2) covered by a nonconductive film. As best seen in FIGS 3 and 4, four electrode arrays are positioned on the substrate so that each array includes a plurality of electrodes connected to conductive patterns (FIG 4:12) and contacts (FIG 4:7). Each array additionally comprises a reference electrode (FIG 4:10). This is disclosed in column 6, lines 32-67. Column 2, lines 35-67 indicate that the cell activity is determined by measuring changes in impedance recorded by the electrodes. Additionally, Sugihara teaches that the electrically conductive traces (FIG 4:12) extend from the opposing ends of the substrate and are in communication with the electrode arrays. This is described in column 6, lines 50-67. Sugihara, however, does not expressly state that the electrodes in each array have a width of more than 1.5 to 10 times the width of the non-conductive area between the electrodes.

The Examiner adds that Facer discloses a device for detecting cells that comprises a non-conductive substrate (FIG 1:12) and a plurality of conductive elements (FIG 14, 16) positioned on the substrate. Paragraph [0012] states that a gap (FIG 1:20) is made in the inner conductor through which biological solutions are allowed to pass. Changes in impedance across the gap are then detected using the conductive elements. Paragraphs [0027]-[0033] give exemplary ranges of sizes and widths for the conductive elements and the gap. Facer suggest that the conductive elements have a width of approximately 40

microns, and the gap constituting the area between the conductive elements is characterized by a width of 1 to 10 microns.

Thus the Examiner argues that at the time of the invention, it would have been obvious to one of ordinary skill in the art to alter Sugahara's device to ensure that the electrode widths were more than 1.5 and less than 10 times the non conductive material width if it was determined through trial and error that this configuration produced the best results. This limitation is considered to be a result of effective variable that is optimized through routine experimentation. This position is supported by Facer, who indicates in paragraph [0033] that electrode width and gap sizes all depend on several considerations that involve engineering tradeoffs. Facer implies that it is know in the art to consider a variety of width sizes in order to produce the best configuration for the current experiment.

<u>Applicants Response</u>

Claims 1-3, 8-10, 36, 40-43 and 72 are not obvious over Sugihara (US 6,132,683) in view of Facer (US 2003/0072549) prior to amendment or after amendment; however, to expedite allowance of the present application Applicants have amended claim 1, from which claims 2, 3, 8-10, 36, 40-43 and 72 depend, to recite, "*each electrode structure comprises at least two electrode elements and the electrode element width is between 1.5 – 15 times the electrode gap width*" and to recite, "*wherein the device has a surface suitable for cell attachment or growth and the cell attachment or growth results in a detectable change in impedance between or among the electrode structures*."

Sugihara (US 6,132,683) was reissued as US RE37,977. Generally, Sugahara incorporates measurement microelectrodes and large reference electrodes for measuring and monitoring cell potential. More specifically, in Sugahara there are a plurality of measurement microelectrodes insulated from one another and a plurality of reference electrodes insulated from one another (Col 2, lns. 40-55 and Claim 1). The reference electrodes in Sugahara have smaller impedance than that of the measurement electrodes (Col. 2, lns 47-50), and typically like Kovacs' design (see above discussion of Kovacs' US 6,051,422 incorporated herein) the reference electrode has a larger area than that of

the measurement microelectrode (Col. 2, lns 62-65; Col. 3, lns 26-35; Col. 6, ln 63- Col. 7, ln.5).

More particularly referring to claim 1 (from which claims 2-3, 8-10, 36, 40-43 and 72 depend), Sugihara does not disclose *a plurality of electrode arrays, each including at least two electrode structures, further wherein each electrode structure comprises at least two electrode elements* and does not disclose *the electrode element width is between 1.5 to 15 times the width of the electrode gap.* In Sugahara, the cell-potential measurement is conducted between reference electrodes and measurement microelectrodes. The reference electrode is shared for multiple measurement electrodes (see Col. 3, lns. 2-5). Thus as in Kovacs' previously, the distance between each measurement electrode and its reference electrode will vary. Overall, it does not appear that Sugahara requires a specified ratio between microelectrode width and gaps between the measurement microelectrode and reference electrode. Sugahara does provide that "*the plural reference electrodes are placed at nearly equal distance from the plural microelectrode region and at intervals of nearly equal angle.*" Col 2, lns. 58-60.

Thus, for Sugahara the importance is that the reference electrode has a smaller electrode impedance and larger surface area than those of the measurement electrodes. There is no incentive nor any stated requirement for a specific ratio between electrode width and gap. Moreover, there is no indication or suggestion that altering the ratio between electrode width to gap to a range of 1.5 – 15 would result in better signals for Sugahara's measurements. Additionally, referring to FIG 4, the gap between the measurement electrode and the reference electrode is significantly larger than the width of the measurement electrode, whereas the present invention includes a gap that is smaller than the width of the electrode element.

Referring to Facer, the Facer technology incorporates CPW and utilizes *one inner conductor flanked by two outer conductors*. Para [0011]. The Examiner refers to Para [0012] which states that a gap (FIG 1:20) is made in an inner conductor through which biological solutions are allowed to pass. Thus, the gap (or passageway) exists between two inner conductor segments, which are electrically connected on one measurement line on the impedance analyzer (the external conductor being the other measurement line).

Applicants herein incorporate by reference Applicants' argument provided above with regard to the gap in Facer.

A combination of Sugahara in view of Facer would not render *the electrode element width is between 1.5 and 15 times the width of the electrode gap* obvious. The above Sugahara arguments and Facer arguments are incorporated herein. In essence, the Examiner argues that Para [0033] of Facer which discloses that gap sizes all depend on several considerations that involve engineering tradeoffs would support varying the width of electrode width to gaps in Sugahara's device. Although the gaps in Sugaraha's device (spacing between measurement microelectrode and reference electrodes) and Facer's device (passageway between an inner connector) are significantly different for the reasons setforth above, even variations in microelectrode width to gap (between measurement microelectrodes to reference electrode) would not render the present invention obvious. As provided in Sugahara, "*the plural reference electrodes are placed at nearly equal distance from the plural microelectrode region and at intervals of nearly equal angle.*" Col 2, lns. 58-60. Futhermore, the importance in Sugahara is that the *reference electrodes have smaller impedance than that of the measurement electrodes* (Col. 2, lns 47-50). Thus for Sugahara it is the 1) size differences between reference electrode and the microelectrode; and 2) the equal spacing of reference electrodes that are of importance and not the microelectrode width to gap ratio. With reference to the actual gap in Sugahara, the gap is larger than the measurement electrode width, whereas in the present invention the gap is smaller than the electrode element width.

In view of the arguments setforth above, which distinguish Applicants' invention from those of Sugahara and Facer, alone or in combination, Applicants respectfully request the rejections under 37 U.S.C. §103(a) be withdrawn from claims 1-3, 8-10, 36, 40-43 and 72.

C. The Examiner has rejected claims 1-3, 5, 7-15, 25, 36, 38-40, 43 and 72 under 35 U.S.C. §103(a) as allegedly being upatentable over Wolf (US 6,280,586) in view of Facer (US 2003/0072549).

The Examiner provides the following arguments in support of the 35 USC §103(a) rejection. With respect to claims 1, 8, 9, 36, 43 and 72, Wolf discloses a device for detecting cells comprising a non-conductive substrate (FIG 2:5) having two opposing ends, and a plurality of electrode arrays positioned on the substrate. Each electrode array comprises at least two electrodes (FIG. 2:10), and electrically conductive traces and connection pads are in communication with the electrode arrays. The electrodes are used to detect impedance chances resulting from attachment of cells to the electrode surface. This is described in colum 2, lines 39-55, column 3, lines 11-28, and colum 7, lines 29-50. Wolf, however, does not expressly state that the electrodes in each array have a width of more than 1.5 to 10 times the width of the non-conductive area between the electrodes.

The Examiner adds that Facer discloses a device for detecting cells that comprises a non-conductive substrate (FIG. 1:12) and a plurality of conductive elements (FIG. 14, 16) positioned on the substrate. Paragraph [0012] states that a gap (FIG 1:20) is made in the inner conductor through which biological solutions are allowed to pass. Changes in impedance across the gap are then detected using the conductive elements. Paragraphs [0027] –[0033] give exemplary ranges of sizes and widths for the conductive elements and the gap. Facer suggests that the conductive elements have a width of approximately 40 microns, and that that gap constituting the area between the conductive elements is characterized by a width of 1 to 10 microns.

Thus, the Examiner argues that at the time of the invention it would have been obvious to one of ordinary skill in the art to alter Wolf's device to ensure that the electrode widths were more than 1.5 and less than 10 times the non conductive material.

Applicants' Response

Claims 1-3, 5, 7-15, 25, 36, 38-40, 43 and 72 are not obvious over Wolf (US 6,280,586) in view of Facer (US 2003/0072549) prior to or after amendment; however, to expedite allowance of the present application Applicants have amended claim 1, from which claims 2, 3, 5, 7-15, 25, 36, 38-40, 43 and 72 depend, to recite, "*each electrode structure comprises at least two electrode elements and the electrode element width is*

between 1.5 – 15 times the width of the electrode gap" and to recite, "*wherein the device has a surface suitable for cell attachment or growth and the cell attachment or growth results in a detectable change in impedance between or among the electrode structures.*"

In Wolf's sensor design,

> "The object is accomplished in that provided between the receptor cells and /or the target cells and the measurement structure is a structured, microporous interlayer which the target cells and/or receptor cells accept as neighbor for adherence." Col 2, ln. 15-18 and claim 1. "The interlayer provided is in particular a marcromolecular porous layer which on the one hand induced adhesion of the cells and on the other hand is proportional in the pores size so as to be permeable for certain ions, molecules or cell areas. By way of example, an SiO2 layer sputtered or applied to the measurement structure, an Al2O3 layer or a Ta2O5 layer can also be provided as the interlayer. By means of the structured interlayer, the electronic measurement structure is conditioned in such a way the target cells or receptor cells accept the measurement structure as neighbour and become better adhere to it. The porosity of the interlayer allows that the ions, molecules or cell areas to be measured of the target cells or receptor cells can reach electrically active areas of the measurement structures." Col. 2, ln 64-Col. 3, ln 30).

The *structured, porous interlayer* between the cells and the sensor surfaces is a very important difference between Wolf's sensor design and Applicants' electrode design, in which there is no need for such structured, porous interlayer. Indeed, had Applicants' design been used in Wolf, the "structured, porous interlayer" would significantly affect the impedance measurements.

Throughout Wolf's invention, there was no discussion of requirement of electrode width. Thus, Wolf does not teach, does not suggest anything along the line of changing the ratio of electrode width to electrode gaps. There was a discussion as for the requirement of electrode spacing where "the spacing of the comb-type or capacitor electrodes is adapted to the diameter of the target cells or …, so that the latter can be in contact with differently polarized capacitor electrodes". Col. 4, ln. 9-13. Thus for Wolf, the importance is the particular relationship between the electrode spacing and the cell size and not the relationship between electrode width and gap.

Although there was a description of varying interdigital capacitors' size (Col. 4, ln. 26-32, and claim 7), Wolf seemed to suggest there was a relationship between the sensitivity and interdigital capacitors' size. But there was no further elaboration of this.

Whilst Wolf discloses the use of interdigital capacitor to measure cell shape and/or cell membrane impedance. It is NOT clear that how interdigital capacitor is used and what measurement would be done on the interdigital capacitor.

With regard to Facer, Applicants' incorporate the Facer arguments setforth above, which includes the Facer technology incorporates CPW and utilizes *one inner conductor flanked by two outer conductors*. Moreover, the gap in Facer is different than the gap in Applicants' invention. In Facer, the gap is a passageway that exists between two inner conductor segments, which are electrically connected on one measurement line on the impedance analyzer (the external conductor being the other measurement line). Therefore applying the Facer gap to Wolf, it appears Wolf would require a gap that acts as a passageway through an electrode that connects to a single impedance line.

With respect to claims 2, 3, 5, 7-15, 25, 36, and 38-40, Applicants incorporate herein Applicants' arguments previously setforth in claim 1, from which claims 2, 3, 5, 7-15, 25, 36, and 38-40 depend.

For the reasons setforth above, claims 1-3, 5, 7-15, 25, 36, 38-40, 43 and 72 are not obvious over Wolf (US 6.280.586) in view of Facer (US 2003/0072549) prior to or after amendment and Applicants' respectfully request the rejections be withdrawn.

D. The Examiner has rejected claims 16-24, 29-32, 34 and 47-50 under 35 U.S.C. §103(a) as allegedly being upatentable over Wolf (US 6,280,586) in view of Facer (US 2003/0072549) and further in view of Wolf (6,376,233).

The Examiners arguments are as follows. Wolf '586 and Facer disclose the apparatus set forth in claims 13 and 15 as set for thin the 35 USC 103 rejection above,

however do not expressly indicate that a plurality of receptacles are disposed on the nonconductive substrate to produce fluid tight containers.

Wolf '233 discloses and apparatus and method for recording electrophysiological activity of biological cells. A plurality of sensors (FIG 4:7) are provided to correspond with the wells (FIG. 3:10) formed by a microtiter plate (FIG 3:11). This is described in column 6, lines 17-30 and in FIGS 3-6. Each sensor array (FIG 4:7a) includes at least one stimulus electrode capable of interacting with cells. Wolf additionally discloses a retaining part (FIG. 3) capable of culturing cells in a region directly above the sensor array.

Thus, the Examiner argues it would have been obvious to provide the device proposed by Wolf, '586 and Facer with a solution retaining part capable of culturing cells. This would have been beneficial because it would have allowed one to encourage cell growth at the integrated electrode, thus removing the need to transport the cell sample from a remote location to the sensor. By eliminating this transportation step, one would be able to increase efficiency and reduce contamination and fluid loss.

<u>Applicants' Response</u>

Claims 16-24, 29-32, 34 and 47-50 are not obvious o over Wolf (US 6,280,586) in view of Facer (US 2003/0072549) in further view of Wolf (US 6,376,233) prior to or after amendment; however, to expedite allowance of the present application Applicants have amended claim 1, from which claims 16-24, 29-32, 34 and 47-50 depend, to recite, "*each electrode structure comprises at least two electrode elements and the electrode element width is between 1.5 – 15 times the width of the electrode gap*" and to recite, "*wherein the device has a surface suitable for cell attachment or growth and the cell attachment or growth results in a detectable change in impedance between or among the electrode structures.*"

Applicants' incorporate herein the arguments setforth above with regard to Wolf (US 6,280,586) and Facer (US 2003/0072549). Moreover, Wolf (US 6,376,233) does not disclose "*each electrode structure comprises at least two electrode elements and the electrode element width is between 1.5 – 15 times the width of the electrode gap*" or "*wherein the device has a surface suitable for cell attachment or growth and the cell*

attachment or growth results in a detectable change in impedance between or among the electrode structures."

Applicants respectfully request the obviousness rejections of Claims 16-24, 29-32, 34 and 47-50 be withdrawn.

D. The Examiner has rejected claim 35 under 35 U.S.C. §103(a) as allegedly being upatentable over Wolf (US 6,280,586) in view of Facer (US 2003/0072549) and further in view of Surridge (US 2003/0116447).

The Examiner alleges the following. Wolf and Facer disclose the apparatus setforth in claim 1 as set forth in the 35 USC 103 rejection above. Additionally, Wolf discloses that the device is produced by providing a non-conductive substrate. Wolf, however, does not state that a conductive film is deposited on the substrate, or that electrodes are patterned using laser ablation of the conductive film.

The Examiner adds that Surridge discloses a substrate that includes a plurality of electrode arrays capable of detecting an analye in a sample solution. Paragraphs [0079]-[0082] indicate that interdigitated electrode arrays (FIG 1) are formed from a conductive film using laser ablation.

Thus, the Examiner argues that at the time of the invention, it would have been obvious to create the electrodes disclosed by Wolf using a conductive film modified by laser ablation process. Surridge states that laser ablation techniques are well known in the art, and that suitable lasers are widespread and commercially available. Surridge suggests that laser ablation techniques employing the use of a conductive film are especially suited for the creation of interdigitated electrodes.

Applicants' Response

Claim 35 is not obvious over Wolf (US 6,280,586) in view of Facer (US 2003/0072549) and further in view of Surridge (US 2003/0116447) prior to or after amendment; however, to expedite allowance of the present application Applicants have amended claim 1, from which claim 35 depends, to recite, "*each electrode structure*

comprises at least two electrode elements and the electrode element width is between 1.5 – 15 times the width of the electrode gap" and to recite, "*wherein the device has a surface suitable for cell attachment or growth and the cell attachment or growth results in a detectable change in impedance between or among the electrode structures.*"

Applicants' incorporate herein the arguments setforth above with regard to Wolf (US 6,280,586) and Facer (US 2003/0072549). Moreover, Surridge (US 2003/0116447) does not disclose "*each electrode structure comprises at least two electrode elements and the electrode element width is between 1.5 – 15 times the width of the electrode gap*" or "*wherein the device has a surface suitable for cell attachment or growth and the cell attachment or growth results in a detectable change in impedance between or among the electrode structures.*"

Applicants respectfully request the obviousness rejection to claim 15 be withdrawn.

E. The Examiner has rejected claim 37 under 35 U.S.C. §103(a) as allegedly being upatentable over Wolf (US 6,280,586) in view of Facer (US 2003/0072549) and further in view of Gomez (US 2003/0157587).

The Examiner provides the following as support for the obviousness rejection. Wolf and Facer disclose the apparatus setforth in claim 1 as set forth in the 35 U.S.C. §103 rejection above, however do not expressly state that capture reagents are immobilized on the surface of the electrodes.

The Examiner adds, Gomez discloses a microelectronic cell sensor that comprises a substrate (FIG 14:54) and a plurality of elctrodes (FIG 14:36) capable of determining the presence of cells in a sample solution. Paragraphs [0087] and [0112] state that antibodies (FIG 14:76) are attached to the electrodes and the substrate in order to selectively bind target bacteria cells (FIG 14:78). A difference in electrical measurements between the electrodes and a reference electrode indicates the presence of target cells in the detection chamber. The binding antibodies disclosed in Gomez are considered to be capable of being isolated from an extracellular matrix, and capable of binding to a cell surface receptor.

Thus the Examiner argues at the time of the invention, it would have been obvious to attach antibodies and other biological molecules to the substrate disclosed by Wolf and Facer. This would have provided an established binding area suitable for cell attachment, and would have allowed one the ability to dictate the location of cells during detection. Gomez teaches in paragraph [0032] that the use of biological binding molecules are beneficial because they can be used to purify a cell sample prior to detection, thereby ensuring that any recording changes in impedance is due solely to the resence of cells rather than contaminants in the solution.

<u>Applicants' Response</u>

Claim 37 is not obvious over Wolf (US 6,280,586) in view of Facer (US 2003/0072549) and further in view of Gomez (US2003/0072549) prior to or after amendment; however, to expedite allowance of the present application Applicants have amended claim 1, from which claim 37 depends, to recite, "*each electrode structure comprises at least two electrode elements and the electrode element width is between 1.5 – 15 times the width of the electrode gap*" and to recite, "*wherein the device has a surface suitable for cell attachment or growth and the cell attachment or growth results in a detectable change in impedance between or among the electrode structures.*"

Applicants' incorporate herein the arguments setforth above with regard to Wolf (US 6,280,586) and Facer (US 2003/0072549). Moreover, Gomez (US2003/0072549) does not disclose "*each electrode structure comprises at least two electrode elements and the electrode element width is between 1.5 – 15 times the width of the electrode gap*" or "*wherein the device has a surface suitable for cell attachment or growth and the cell attachment or growth results in a detectable change in impedance between or among the electrode structures.*"

Applicants respectfully request the rejection to claim 37 be withdrawn.

III. Response to Provisional Double Patenting Rejections

A. The Examiner has provisionally rejected claims 1, 4, 25, 38-40 and 72 on the ground of nonstatutory obvious-type double patenting as being unpatentable over claims 1, 2 and 58 of copending Application No. 11/055,639 in view of Facer (US 2003/0072549).

The Examiner alleges the claims of Application No. 11/055,639 disclose a device and method for detecting cells that comprises a non-conductive substrate and a plurality of electrode arrays wherein each electrode array comprises at least two or more electrodes. Electrically conductive traces and connection pads are provided. The claims of Application no. 11/055,639, however, do not state specifics regarding electrode width and positioning.

The Examiner adds Facer discloses the device as previously described. Paragraphs [0027]-[0033] give exemplary ranges of sizes and widths for the conductive elements and the gap. Facer suggests that the conductive elements have a width of approximately 40 microns, and that the gap constituting the area between conductive elements is characterized by a width of 1 to 10 microns.

Thus, the Examiner argues at the time of the invention it would have been obvious to one of ordinary skill in the art to alter the device of Application No. 11/055,639 to ensure that the electrode widths were more than 1.5 and less than 10 times the non conductive material width if it was determined through trial and error that this configuration produced the best results. This limitation is considered to be a result effect variable that is optimized through routine experimentation. This position is supported by Facer, who indicates in paragraph [0033] that electrode width and gap sizes all depend on several considerations that involve engineering tradeoffs. Facer implies that it is known in the art to consider a variety of width sizes in order to produce the best configuration for the current experiment.

Applicants' Response

Claims 1, 4, 25, 38-40 and 72 are patentably distinct over claims 1, 2 and 58 in view of Facer (US 200//0072549) prior to or after amendment; however, to expedite allowance of the present application Applicants have amended claim 1, from which claims 4, 25, 38-40 and 72 depend, to recite, "*each electrode structure comprises at least two electrode elements and the electrode element width is between 1.5 – 15 times the width of the electrode gap*".

Claims 1, 2 and 58 of copending Application No. 11/055,639 do not provide *each electrode structure comprises at least two electrode elements and the electrode element width is between 1.5 – 15 times the electrode gap width.*

Applicants' incorporate herein the arguments setforth above with regard to Facer (US 2003/0072549). Thus, Facer does not disclose "*each electrode structure comprises at least two electrode elements and the electrode element width is between 1.5 – 15 times the width of the electrode gap*".

In view of Applicants' response, Applicants respectfully request the provisional double patenting rejection of claims 1, 4, 25, 38-40 and 72 be withdrawn.

B. The Examiner has provisionally rejected claims 1, 4, 25, 38-40 and 72 on the ground of nontstatutory obvious-type double patenting as being unpatentable over claims 51, 72 and 75 of copending Application No. 10/987,732 in view of Facer (US 2003/0072549).

The Examiner alleges the claims of Application No. 10/987,732 disclose a device and method for detecting cells that comprises a non-conductive substrate and a plurality of electrode arrays wherein each electrode array comprises at least two or more electrodes. The use of an impedance analyzer is additionally described. Conductive traces and bonding pads are considered to be well known in the art. The claims of Application No. 10/987,732, however, doe not state specifics regarding the electrode width and positioning.

The Examiner adds, Facer discloses the device as previously described above. Paragraphs [0027]-[0033] give exemplary ranges of sizes and widths for the conductive elements and the gap. Facer suggests that the conductive elements have a width of approximately 40 microns, and the gap constituting the area between the conductive elements is characterized by a width of 1 to 10 microns.

Thus the Examiner argues at the time of the invention, it would have been obvious to one of ordinary skill in the art to alter the device of Application No. 10/987,732 to ensure that the electrode widths were more than 1.5 and less than 10 times the non-conductive material width if it was determined through trial and error that this configuration produced the best results. This limitation is considered to be a result effective variable that is optimized through routine experimentation. This position is supported by Facer, who indicates in paragraph [0033] that electrode width and gap sizes all depend on several considerations that involve engineering tradeoffs. Facer implies that it is known in the art to consider a variety of width sizes in order to produce the best configuration for the current experiment.

<u>Applicants' Response</u>

Claims 1, 4, 25, 38-40 and 72 are patentably distinct over claims 51, 72 and 75 in view of Facer (US 200//0072549) prior to or after amendment; however, to expedite allowance of the present application Applicants have amended claim 1, from which claims 4, 25, 38-40 and 72 depend, to recite, "*each electrode structure comprises at least two electrode elements and the electrode element width is between 1.5 – 15 times the width of the electrode gap*".

Claims 51, 72 and 75 of copending Application No. 10/987732 do not provide *each electrode structure comprises at least two electrode elements and the electrode element width is between 1.5 – 15 times the width of the electrode gap.*

Applicants' incorporate herein the arguments setforth above with regard to Facer (US 2003/0072549). Thus, Facer does not disclose "*each electrode structure comprises at least two electrode elements and the electrode element width is between 1.5 – 15 times the width of the electrode gap*".

In view of Applicants' response, Applicants respectfully request the provisional double patenting rejection of claims 1, 4, 25, 38-40 and 72 be withdrawn.

CONCLUSION

Applicants respectfully submit that all rejections be withdrawn and request an allowance be granted for present application.

Respectfully submitted,

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